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Predictors of cardiovascular events in a contemporary population with impaired glucose tolerance: an observational analysis of the Nateglinide and Valsartan in impaired glucose tolerance outcomes research (NAVIGATOR) trial

David Preiss,[1] Laine E Thomas,[2] Jie-Lena Sun,[2] Steven M Haffner,[3] Rury R Holman,[4] Eberhard Standl,[5] Lawrence A Leiter,[6] Theodore Mazzone,[7] Guy E Rutten,[8] Gianni Tognoni,[9] Felipe A Martinez,[10] Fu-Tien Chiang,[11] Robert M Califf,[12] John J McMurray[1]

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For numbered affiliations see end of article.

Correspondence to
Dr David Preiss;
david.preiss@glasgow.ac.uk

ABSTRACT

Objectives: Risk factors for cardiovascular events are well established in general populations and those with diabetes but have been sparsely studied in impaired glucose tolerance (IGT). We sought to identify predictors of (1) a composite cardiovascular outcome (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) and (2) cardiovascular death, among patients with IGT.

Design: We studied participants enrolled in the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial. Predictors of cardiovascular events were identified in observational analyses.

Setting: Clinical trial participants in 40 countries.

Participants: 9306 participants with biochemically confirmed IGT at high risk of cardiovascular events participated in NAVIGATOR.

Primary and secondary outcome measures: Cox proportional hazard regression models were constructed using variables (demographic data, medical history, clinical features, biochemical results and ECG findings) recorded at baseline to identify variables associated with and predictive of cardiovascular events.

Results: Over 6.4 years, 639 (6.9%) participants experienced a cardiovascular event, and 244 (2.6%) cardiovascular death. While predictors of both outcomes included established risk factors such as existing cardiovascular disease, male gender, older age, current smoking status and higher low-density lipoprotein cholesterol, other variables such as reduced estimated glomerular filtration rate, previous thromboembolic disease, atrial fibrillation, higher urinary albumin/creatinine ratio and chronic obstructive pulmonary disease were also important predictors. Glycaemic measures were not predictive of cardiovascular events. c-Statistics for predicting cardiovascular events and cardiovascular death were 0.74 and 0.82, respectively. This compares with c-statistics for cardiovascular events and cardiovascular death of 0.65 and 0.71, respectively, using the classical Framingham risk factors of age, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, treatment for hypertension and smoking status.

ARTICLE SUMMARY

Article focus

- Predictors of cardiovascular events have been intensively studied in general populations and in patients with diabetes but less well studied in those with impaired glucose tolerance (IGT).
- The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study is the largest trial yet conducted in those with biochemically confirmed IGT and major cardiovascular events were adjudicated endpoints, providing an opportunity to study the predictors of risk.

Key messages

- Predictors of cardiovascular events in IGT included established risk factors such as existing cardiovascular disease, male gender, older age, current smoking status and higher low-density lipoprotein cholesterol.
- Other variables such as reduced estimated glomerular filtration rate, previous thromboembolic disease, atrial fibrillation, higher urinary albumin/creatinine ratio and chronic obstructive pulmonary disease were also important predictors.
- Glycaemic measures (glycated haemoglobin, fasting plasma and 2 h glucose) were not predictive of cardiovascular events.

ARTICLE SUMMARY

Strengths and limitations of this study

- NAVIGATOR was a prospective study that included over 9000 participants with biochemically confirmed IGT and accumulated a large number of cardiovascular endpoints.
- Participants in the study were well phenotyped at baseline in the study.
- The results from NAVIGATOR may not be applicable to all with IGT as participants were a high-risk population based on other cardiovascular risk factors.

Conclusions: The most powerful independent predictors of cardiovascular events in IGT included both established risk factors and other variables excluding measures of glycaemia, allowing effective identification of high-risk individuals.

Individuals with impaired glucose tolerance (IGT) are at an elevated risk of cardiovascular events compared with normoglycaemic individuals.[1 2] Consequently, identification of cardiovascular risk factors in subjects with IGT, an increasingly common condition,[3] should improve risk prediction of cardiovascular events and help target interventions to reduce risk. Cardiovascular risk factors are already well established in general populations and in patients with diabetes. Algorithms to predict risk of future cardiovascular events in the general population commonly include classical risk factors such as older age, male sex, smoking, elevated blood pressure, dyslipidaemia, diabetes and family history of premature cardiovascular disease.[4] Recently, other factors such as microalbuminuria, glycated haemoglobin (HbA1c), atrial fibrillation, chronic kidney disease, lower-socioeconomic status, abdominal obesity and higher body mass index have been added to improve risk estimation.[5] Predictive models in subjects with established diabetes include these and additional variables like diabetes duration, anthropometric measures and presence and severity of microvascular complications.[6–9] However, risk factors independently associated with cardiovascular events have not been studied in detail in IGT and little is known about the distribution of absolute risk of cardiovascular events in IGT.

The aims of this study were to identify independent predictors of two outcomes, namely a composite cardiovascular endpoint (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) and cardiovascular death, respectively, in individuals with IGT, to clarify the distribution of absolute risk of events in this population and to assess the use of cardiovascular risk-reducing therapies according to absolute risk categories using data from the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial.

METHODS

NAVIGATOR (ClinicalTrials.gov number, NCT00097786) was a double-blinded randomised clinical trial with a two-by-two factorial design which assessed the ability of two agents, nateglinide and valsartan, to respectively reduce major cardiovascular events and new-onset diabetes in participants with IGT. Details of the trial including the protocol, results and design were published previously.[10–12] In brief, a total of 9306 participants from 40 countries participated in the trial for a median of 6.4 years. Each participant was randomised to treatment with nateglinide or placebo plus valsartan or placebo, and participants received a lifestyle modification programme.

Participants

On the basis of general criteria including age and history of cardiovascular disease, possible research participants were asked to attend screening clinics to formally assess their potential enrolment. Men and women with IGT were eligible if they had one or more cardiovascular risk factors and were aged ≥55 years or if they had established cardiovascular disease and were aged ≥50 years. Inclusion and exclusion criteria are described in previous publications.[10–12] Potentially eligible subjects underwent an oral 75 g glucose tolerance test (OGTT) and IGT was defined as a 2 h postchallenge glucose value of 7.8–11.0 mmol/l (and fasting plasma glucose of 5.3–6.9 mmol/l). Subjects taking an ACE inhibitor for hypertension (patients taking an ACE inhibitor for other conditions (coronary artery disease, left ventricular dysfunction, macroalbuminuria, peripheral arterial disease, stroke or transient ischaemic attack) were not excluded) or an angiotensin II-receptor blocker (ARB) who were unable or unwilling to stop the drug were excluded. Those taking an ACE inhibitor or ARB for these other conditions were required to stop treatment at least 4 weeks prior to participation. All NAVIGATOR participants provided written informed consent.

Cardiovascular endpoints

We focused on the prediction of two cardiovascular endpoints: (1) a composite cardiovascular outcome of cardiovascular mortality, non-fatal myocardial infarction or non-fatal stroke (this differs from the extended composite cardiovascular outcome used as the primary endpoint in the trial) and (2) cardiovascular death. Endpoints were adjudicated by an independent committee blinded to treatment allocation.

Statistical analysis

Continuous baseline variables were summarised as mean±SD, except where noted otherwise. Between groups, comparisons were performed using t tests for normally distributed data or non-parametric tests (Wilcoxon rank sum) otherwise. Categorical variables were summarised as counts and percentages and were compared using χ^2 tests or Fisher's exact test.

Prognostic model building: Data from all NAVIGATOR participants were included to construct separate models for (1) the composite cardiovascular outcome and

(2) cardiovascular death. Thirty-eight candidate variables collected at baseline, consisting of demographics, clinical measurements, medical history, investigator reported ECG (normal, clinically insignificant abnormality or clinically significant abnormality) and laboratory results, were included (listed in table 1). Cox proportional hazard regression models were developed to evaluate the relationships between these candidate variables and both cardiovascular outcomes, and these were added to the model by forward selection at $p<0.05$. Missing data were handled by single and multiple imputation, which provided consistent results and single imputation is reported herein. Less than 3% of data were missing for all variables except for HbA1c where 15% were missing. Variables were checked for linearity and proportional hazards. Linear splines were used to account for non-linear relationships of relevant continuous variables with cardiovascular outcomes. The statistical strength of the contribution of each variable to prediction of the cardiovascular outcome was expressed as the p value corresponding to the Wald χ^2 statistic, a measure allowing direct comparison of the predictive information provided by each variable. In sensitivity analyses, study treatments (nateglinide and valsartan) were forced into the models for both endpoints. Models using only classical-risk factors from the Framingham equations (age, total cholesterol, high-density lipoprotein (HDL), systolic blood pressure (SBP), treatment for hypertension and smoking status) were also developed to allow comparison with the variable-rich models.

A calibration plot comparing predicted and observed risk of a cardiovascular event was generated to assess the risk distribution in the NAVIGATOR trial population.

Assessment of appropriateness of care

We aimed to assess whether participants at progressively higher risk of cardiovascular events were treated more intensively with risk-reducing agents. Participants were divided into those with and without cardiovascular disease at baseline. Those without baseline cardiovascular disease were further divided into low (<2.5% with the composite cardiovascular outcome per 5 years), intermediate (2.5–10% per 5 years) and high (>10% per 5 years) risk based on subsequent occurrence of cardiovascular events. Prescriptions of cardiovascular risk lowering medications at baseline were tabulated to allow direct comparison.

p Values <0.05 were considered statistically significant and all p values were two sided. Analyses were conducted using SAS V.9.2 software (Chicago, Illinois, USA). There are no additional data available.

RESULTS

Baseline results for the 9306 participants in NAVIGATOR are provided in table 1, divided into those who did and did not experience the composite cardiovascular outcome. Average age was 64 years, 6131 (66%) had no history of cardiovascular disease at baseline, and mean HbA1c was 5.8%. During median follow-up of 6.4 years, 639 (6.9%) experienced the composite cardiovascular outcome (event rate 5.9% (95% CI 5.4% to 6.4%) averaged over 5 years) and 244 (2.6%) participants died from cardiovascular causes (event rate 2.0 (95% CI 1.7 to 2.3) averaged over 5 years). When limited to the subgroup with no history of cardiovascular disease, 248 (4.0%) experienced a composite cardiovascular outcome event.

Risk factors independently associated with the composite cardiovascular outcome

In the multivariable Cox model, history of coronary heart disease (present in 28%) was the strongest predictor and was associated with a doubling of risk (see table 2). Male sex was associated with 89% increase in cardiovascular risk while older age was associated with 32% higher risk per decade. Other major predictors included current smoking status, physician-reported clinically significant abnormality on ECG, higher low-density lipoprotein (LDL) cholesterol, history of cerebrovascular disease and lower estimated glomerular filtration rate (eGFR). Other variables independently associated with cardiovascular events were history of peripheral arterial disease, history of pulmonary embolism or deep venous thrombosis, higher urine albumin-to-creatinine ratio (UACR), geographic area (Latin America vs North America), higher pulse pressure, history of chronic obstructive pulmonary disease (COPD), black race (vs all other races), history of heart failure, lower haemoglobin, lower serum sodium, higher waist circumference and atrial fibrillation. None of fasting plasma glucose, 2 h postchallenge glucose or HbA1c was independently associated with the composite cardiovascular outcome. The c-statistic for this variable-rich prognostic model was 0.74. When study treatments were forced into the model, neither displayed a significant association and the impact on the predictive capabilities of the other variables was negligible (data not shown). The c-statistic for a predictive model including only classical risk factors (age, total cholesterol, HDL-cholesterol, SBP, treatment for hypertension and smoking status) was 0.65.

Risk factors independently associated with cardiovascular death

Older age was the strongest predictor of cardiovascular death (77% higher risk per 10 years; see table 3). Both history of coronary heart disease and the presence of congestive heart failure (present in 4% of participants) were associated with a doubling in risk. Other variables independently associated with cardiovascular death were geographical area (Latin America vs North America, Other vs North America), male sex, current smoking status, clinically significant or insignificant abnormalities on ECG, lower eGFR, higher UACR, history of cerebrovascular disease, atrial fibrillation, lower haemoglobin, history of COPD, peripheral arterial disease and history of renal dysfunction. The c-statistic for this variable-rich

Table 1 Baseline characteristics of 9306 participants with impaired glucose tolerance in the NAVIGATOR trial stratified by occurrence of events, namely cardiovascular death, non-fatal myocardial infarction and non-fatal stroke

Variable*	All	Experienced cardiovascular event during trial		p Value
		No	Yes	
N	9306	8667	639	
Age (years)	63.8 (6.8)	63.6 (6.8)	66.0 (7.6)	<0.001
Male gender	4595 (49%)	4169 (48)	426 (67)	<0.001
Race				
Black	236 (3)	213 (3)	23 (4)	0.15
White	7734 (83)	7199 (83)	535 (84)	–
Asian	613 (7)	580 (7)	33 (5)	–
Other	723 (8)	675 (8)	48 (8)	–
Region				
North America	2146 (23)	2006 (23)	140 (22)	0.01
Europe	4909 (53)	4590 (53)	319 (50)	–
Asia	552 (6)	522 (6)	30 (5)	–
Latin America	1406 (15)	1281 (15)	125 (20)	–
Other	293 (3)	268 (3)	25 (4)	–
Current smoker	1025 (11)	922 (11)	103 (16)	<0.001
Medical history				
Coronary heart disease†	2626 (28)	2295 (27)	331 (52)	<0.001
Cerebrovascular disease‡	736 (8)	638 (7)	98 (15)	<0.001
Peripheral arterial disease§	309 (3)	254 (3)	55 (9)	<0.001
Chronic obstructive pulmonary disease	451 (5)	385 (4)	66 (10)	<0.001
Heart failure	331 (4)	269 (3)	62 (10)	<0.001
Hypertension	7216 (78)	6710 (77)	506 (79)	0.30
Renal dysfunction¶	90 (1)	66 (1)	24 (4)	<0.001
Pulmonary embolism or deep venous thrombosis	129 (1)	108 (1)	21 (3)	<0.001
Family history of premature coronary heart disease	1544 (17)	1427 (17)	117 (18)	0.23
Family history of diabetes	3547 (38)	3324 (38)	223 (35)	0.08
Clinical features				
Weight (kg)	83.6 (17.2)	83.5 (17.2)	84.9 (17.4)	0.04
Body mass index (kg/m^2)	30.5 (5.4)	30.5 (5.4)	30.3 (5.4)	0.17
Waist circumference (cm)	101.1 (13.6)	100.9 (13.6)	103.2 (13.8)	<0.001
Height (cm)	165.4 (9.9)	165.3 (9.9)	167.3 (9.7)	<0.001
Systolic blood pressure (mm Hg)	139.7 (17.5)	139.5 (17.2)	141.6 (20.1)	0.04
Diastolic blood pressure (mm Hg)	82.6 (10.2)	82.6 (10.2)	82.0 (10.9)	0.10
Pulse pressure (mm Hg)	57.1 (13.9)	56.9 (13.7)	59.6 (15.7)	<0.001
Left ventricular hypertrophy	268 (3)	236 (3)	32 (5)	0.001
Heart rate (bpm)	70.1 (10.6)	70.2 (10.5)	69.1 (11.6)	0.004
Atrial fibrillation or flutter	356 (4)	298 (3)	58 (9)	<0.001
Laboratory				
Fasting glucose (mmol/l)	6.1 (0.5)	6.1 (0.5)	6.1 (0.5)	0.83
2 h glucose (mmol/l)	9.2 (0.9)	9.2 (0.9)	9.3 (0.9)	0.01
HbA1c (%)	5.8 (0.4)	5.8 (0.4)	5.9 (0.5)	<0.001
eGFR (ml/min/1.73 m^2)	80.5 (18.1)	80.8 (18.0)	76.3 (19.9)	<0.001
Urine albumin/creatinine ratio (log units)	0.1 (1.2)	0.1 (1.1)	0.4 (1.3)	<0.001
LDL cholesterol (mmol/l)	3.3 (0.9)	3.3 (0.9)	3.3 (1.0)	0.72
HDL cholesterol (mmol/l)	1.3 (0.3)	1.3 (0.3)	1.2 (0.3)	<0.001
Triglycerides (mmol/l)	1.9 (1.1)	1.9 (1.1)	2.0 (1.1)	0.11
Haemoglobin (g/l)	147 (13)	147 (13)	147 (14)	0.19
Sodium (mmol/l)	142.4 (2.5)	142.4 (2.5)	142.4 (2.8)	0.76
ECG				
Normal	4525 (49)	4316 (50)	209 (33)	<0.001
Clinically insignificant abnormality	3326 (36)	3090 (36)	236 (37)	–
Clinically significant abnormality	1455 (16)	1261 (15)	194 (30)	–

*Not listed in table but also included in predictive models: potassium, WBC, platelet count.
†Previous myocardial infarction, angina, positive stress test, coronary revascularisation.
‡Stroke, transient ischaemic attack.
§Limb or foot amputation, intermittent claudication, limb arterial bypass procedure.
¶Defined using a combination of preferred and low-level MedDRA terms selected by medically qualified personnel. Data presented as (N (%) or mean (SD)).
eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAVIGATOR, Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; WBC, white blood cell.

Table 2 Predictors of the composite cardiovascular outcome in NAVIGATOR participants as identified in a multivariable Cox proportional hazard stepwise selection model

Variable	HR (95% CI)	Wald χ^2	p Value
Coronary heart disease*	2.10 (1.76 to 2.50)	68.8	<0.0001
Gender (male vs female)	1.89 (1.55 to 2.29)	40.9	<0.0001
Age (per 10 years)	1.32 (1.17 to 1.48)	21.4	<0.0001
Current smoker	1.64 (1.32 to 2.04)	19.5	<0.0001
Significantly abnormal vs normal ECG	1.59 (1.28 to 1.97)	17.6	<0.0001
LDL cholesterol	1.19 (1.09 to 1.30)	15.9	<0.0001
Cerebrovascular disease*	1.56 (1.25 to 1.95)	15.5	<0.0001
eGFR (per 10 unit decrease below 60 ml/min/1.73 m^2)	1.31 (1.13 to 1.51)	12.6	0.0004
Peripheral artery disease*	1.65 (1.24 to 2.19)	11.6	0.0007
Pulmonary embolism/deep vein thrombosis	2.12 (1.36 to 3.31)	10.9	0.0010
Urine albumin/creatinine ratio (log units)	1.10 (1.03 to 1.17)	9.1	0.0025
Latin America vs North America	1.48 (1.15 to 1.92)	9.0	0.0027
Pulse pressure (per 1 mm Hg)	1.01 (1.00 to 1.01)	7.8	0.0051
Chronic obstructive pulmonary disease	1.44 (1.10 to 1.88)	7.1	0.0077
Black vs all other races	1.75 (1.13 to 2.71)	6.3	0.0123
Heart failure	1.43 (1.07 to 1.90)	5.9	0.0150
Haemoglobin (per 10 g/l decrease)	1.09 (1.02 to 1.16)	5.8	0.0158
Sodium (1 unit decrease below 140 mmol/l)	1.11 (1.02 to 1.20)	5.5	0.0185
Waist circumference (per 10 cm)	1.08 (1.01 to 1.15)	5.4	0.0197
Atrial fibrillation or flutter	1.34 (1.01 to 1.79)	4.0	0.0463
Other vs North America	1.40 (0.91 to 2.15)	2.3	0.1285
Insignificantly abnormal vs normal ECG	1.11 (0.91 to 1.35)	1.1	0.3000
Europe vs North America	0.92 (0.74 to 1.14)	0.6	0.4391
Asia vs North America	0.90 (0.59 to 1.37)	0.2	0.6268

*For definitions see table 1 footnote.
eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; NAVIGATOR, Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research.

Table 3 Predictors of cardiovascular death in NAVIGATOR participants as identified in a multivariable Cox proportional hazard stepwise selection model

Variable	HR (95% CI)	Wald χ^2	p Value
Age (per 10 years)	1.77 (1.47 to 2.12)	37.6	<0.0001
Latin America vs North America	2.68 (1.82 to 3.96)	24.6	<0.0001
Coronary heart disease*	2.04 (1.53 to 2.72)	23.9	<0.0001
Heart failure	2.27 (1.56 to 3.30)	18.3	<0.0001
Gender (male vs female)	1.90 (1.41 to 2.57)	17.5	<0.0001
Current smoker	2.00 (1.41 to 2.83)	15.1	0.0001
Significantly abnormal vs normal ECG	2.01 (1.38 to 2.92)	13.3	0.0003
eGFR (per 10 ml/min/1.73 m^2 decrease below 60 ml/min/1.73 m^2)	1.42 (1.16 to 1.75)	11.1	0.0009
Urine albumin/creatine ratio (log units)	1.16 (1.06 to 1.27)	10.1	0.0015
Cerebrovascular disease*	1.72 (1.23 to 2.40)	10.0	0.0016
Atrial fibrillation or flutter	1.81 (1.24 to 2.65)	9.4	0.0021
Haemoglobin (per 10 g/l decrease)	1.15 (1.04 to 1.27)	7.4	0.0066
Chronic obstructive pulmonary disease	1.70 (1.16 to 2.49)	7.4	0.0066
Insignificantly abnormal vs normal ECG	1.60 (1.13 to 2.26)	7.1	0.0076
Other vs North America	2.32 (1.23 to 4.40)	6.7	0.0098
Peripheral artery disease*	1.66 (1.08 to 2.55)	5.4	0.0203
Renal dysfunction	1.97 (1.09 to 3.56)	5.0	0.0250
Asia vs North America	0.66 (0.30 to 1.47)	1.0	0.3090
Europe vs North America	1.05 (0.74 to 1.48)	0.1	0.7993

*For definitions see table 1 footnote.
eGFR, estimated glomerular filtration rate; NAVIGATOR, Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research.

prognostic model was 0.82. When study treatments were forced into the model, neither displayed a significant association and the impact on the predictive capabilities of the other variables was negligible (data not shown). The c-statistic for a predictive model including only classical risk factors was 0.71.

Distribution of risk in the NAVIGATOR trial population

A calibration plot which allows comparison of the predicted and observed risk of experiencing a cardiovascular event is provided in online supplementary figure S1. Approximately 37.5% of participants were at greater than 5% calculated risk of a cardiovascular event over 5 years, and 3.5% were at greater than 20% calculated risk of an event over 5 years. Although the model was developed for all NAVIGATOR participants, it could also be applied to those with no known cardiovascular disease, as indicated by the general lack of interaction for variables between those with and without cardiovascular disease at baseline (see online supplementary table S1) and by the good model calibration for the primary prevention group (see online supplementary figure S2).

Use of cardiovascular risk reducing agents according to calculated cardiovascular risk

Baseline characteristics of NAVIGATOR participants divided into those with and without baseline cardiovascular disease, with the latter group split further into those at low, intermediate and high (>10%) calculated risk, are provided in the online supplementary table S2. There were significant differences between those without cardiovascular disease at high risk compared to those at low and intermediate risk as expected.

Prescription of antihypertensive agents at baseline increased progressively from 63% in the low-risk primary prevention group to 86% in those with cardiovascular disease (see table 4). β-Blockers were used twice as commonly in patients with established cardiovascular disease as in the lowest risk category of those without. Similarly, ACE inhibitors were used relatively much more commonly in those with established cardiovascular disease than in low-risk patients without (although their overall use was low in absolute terms, possibly because of the trial exclusion criteria). Aspirin was used for secondary prevention in 69% of participants with cardiovascular disease whereas relatively few participants took aspirin for primary prevention. For secondary prevention 57% of participants were on lipid-lowering therapy. There was an inverse relationship between use of lipid-lowering therapy and calculated cardiovascular risk in the primary prevention cohort; 33%, 26% and 21% were on these agents in the low-risk, intermediate-risk and high-risk groups, respectively.

DISCUSSION

In this analysis of NAVIGATOR, a large randomised trial in subjects with IGT at an elevated risk of cardiovascular events, risk factors most strongly associated with future cardiovascular events largely reflected the same factors identified in general populations and in patients with diabetes.[1 2 5–8] However, neither fasting plasma glucose, 2 h postchallenge glucose nor HbA1c was independently associated with incident cardiovascular events. Approximately 40% of participants in NAVIGATOR were at greater than 5% 5-year risk. While treatment at baseline with antihypertensive agents and other risk-reducing drugs increased progressively with increasing predicted risk, the trend in use of lipid-lowering therapy was in the opposite direction (and use of this treatment and other preventive drug therapies such as aspirin therapy were relatively uncommon overall). This may indicate that physicians are unsure about how to risk-stratify patients with IGT and that a risk-stratification tool would be useful for this growing population's contribution to the overall burden of cardiovascular disease.

Several studies have estimated the increased cardiovascular risk of individuals with IGT, compared with

Table 4 Use of cardiovascular risk-lowering agents at baseline according to estimated cardiovascular risk (n (%))

	History of cardiovascular disease at baseline?				
	No				
Medications	Low risk* (n=2398)	Intermediate risk* (n=3580)	High risk* (n=153)	Yes (n=3175)	p Value for trend
α-Blocker	101 (4.2)	264 (7.4)	13 (8.5)	199 (6.3)	<0.001
ACE inhibitor	27 (1.1)	77 (2.2)	10 (6.5)	562 (17.7)	<0.001
β-Blocker	712 (29.7)	1056 (29.5)	53 (34.6)	1845 (58.1)	<0.001
Calcium channel blocker	603 (25.1)	1172 (32.7)	57 (37.3)	1180 (37.2)	<0.001
Diuretic	750 (31.3)	1194 (33.4)	57 (37.3)	959 (30.2)	0.018
Any antihypertensive	1511 (63.0)	2464 (68.8)	112 (73.2)	2729 (86.0)	<0.001
Aspirin	429 (17.9)	759 (21.2)	42 (27.5)	2195 (69.1)	<0.001
Lipid-lowering agent	794 (33.1)	942 (26.3)	32 (20.9)	1809 (57.0)	<0.001

*Cardiovascular risk derived from the prognostic model derived in NAVIGATOR; low risk refers to <5% experiencing the composite cardiovascular event over 10 years, intermediate risk 5–20% and high risk >20%.
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subjects with normoglycaemia. In a recent systematic review, IGT was associated with 20% higher cardiovascular risk compared with normoglycaemia after adjustment for established cardiovascular risk factors (age, smoking status, blood pressure and lipid levels)[2] and data from the DECODE study showed a 34% increase in the risk of cardiovascular death in individuals with IGT after adjustment for established risk factors.[1] In NAVIGATOR participants, expected independent predictors of events included previous history of cardiovascular disease, male gender, older age, current smoker status, higher LDL cholesterol and higher pulse pressure. Regarding renal biomarkers, each of lower eGFR and higher UACR were also independently associated with cardiovascular events. We found a number of other variables to be predictive of cardiovascular events, including COPD, atrial fibrillation, lower haemoglobin and previous pulmonary embolism or deep venous thrombosis, some of which have also been associated with cardiovascular risk in diabetes populations.[8] A relationship between COPD and cardiovascular events has been reported previously[13 14] and, while this association is not fully explained, smoking is clearly a common risk factor. Atrial fibrillation has been shown to improve risk prediction in both general populations and in type 2 diabetes and has recently been incorporated into risk algorithms.[5] Anaemia has been associated with higher cardiovascular risk, particularly in patients with chronic kidney disease, but results have been mixed in studies of unselected populations.[15–18] Survivors of hospital admissions for pulmonary embolism have been shown to have a substantial risk for subsequent cardiovascular death in cohort studies.[19] Participants from Latin America were also at particularly an elevated risk.

Studies of patients with diabetes and general populations have suggested that measures of glycaemia, especially higher HbA1c and postchallenge glucose, are associated with higher cardiovascular risk.[1 6 20] In our study, no measure of glycaemia (HbA1c, fasting plasma glucose, 2 h postchallenge glucose) was independently associated with or predictive of cardiovascular events. This may reflect the design of NAVIGATOR which specifically recruited individuals with IGT, with the result that the ranges of values for the three glycaemic variables were relatively narrow. This suggests that while identifying individuals with IGT may be of clinical value, refining risk prediction by further categorising according to measures of glycaemia is probably not clinically worthwhile. Interestingly, while higher pulse pressure was predictive of events, other related variables (systolic and diastolic blood pressure, hypertension and left ventricular hypertrophy) were not predictive. HDL cholesterol levels and heart rate also failed to improve prediction.

As expected, the proportion of individuals treated with antihypertensive therapies increased progressively according to calculated cardiovascular risk and was highest in those with known cardiovascular disease. Recent meta-analyses have suggested that aspirin therapy is best targeted at those with established cardiovascular disease[21] and data for the NAVIGATOR participants largely reflected this. However, the use of lipid-lowering therapies for secondary prevention was relatively low (57%) which may reflect variations between participating countries in statin use, the fact that statin use at the start of NAVIGATOR was not as widespread as it is now, and the absence of data for cholesterol levels prior to the start of lipid-lowering therapies. In those with no history of cardiovascular disease, the use of lipid-lowering therapies was sparse in those at highest calculated risk (21%). This suggests that there is a need to better identify and/or treat those with IGT at highest risk, something that may be better achieved when considering classical cardiovascular risk factors as well as the many other risk factors identified here.

This study has a number of strengths and weaknesses. It is the first study to examine predictors of cardiovascular risk specifically in individuals with IGT on a large scale. Cardiovascular events were adjudicated independently. IGT was confirmed biochemically in a standardised manner though only a single OGTT was performed at baseline. However, NAVIGATOR participants either had a history of cardiovascular disease or were at high risk and so these data may not be directly applicable to all individuals with IGT. We also examined a composite cardiovascular endpoint and study of specific cardiovascular endpoints may have provided additional information, although statistical power would be limited. There were relatively few cardiovascular deaths with the result that applying a predictive model with many variables had the potential of over-fitting the model. Finally, we were not able to validate our results by comparison with participants from a separate study.

In summary, the most powerful independent predictors of cardiovascular events in a trial population with IGT at high cardiovascular risk included classical risk factors as well as other factors such as reduced glomerular filtration rate, higher urine albumin excretion and pre-existing thromboembolic disease, atrial fibrillation, heart failure and chronic obstructive pulmonary disease. Prognostic models showed that consideration of these variables would allow effective identification of high-risk individuals with IGT. However, measures of glycaemia were not independently associated with cardiovascular events. Finally, our data identify a need to better identify patients with IGT at high-cardiovascular risk to facilitate more aggressive management with statins and other cardiovascular risk-reducing agents.

Author affiliations
[1]BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK
[2]Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina, USA
[3]Department of Medicine, Baylor College of Medicine, Houston, Texas, USA
[4]Diabetes Trials Unit, University of Oxford, Oxford, UK
[5]Diabetes Research Group, Helmholtz Centre, Munich, Germany

[6]Division of Endocrinology and Metabolism, St Michael's Hospital, Toronto, Canada
[7]Department of Medicine, University of Illinois, Chicago, Illinois, USA
[8]Department of General Practice, Julius Center for Health Sciences and Primary Care, UMC, Utrecht, The Netherlands
[9]Department of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud, Santa Maria Imbaro, Chieti, Italy
[10]Cordoba National University, Cordoba, Argentina
[11]Department of Laboratory Medicine, College of Medicine, National Taiwan University, Taiwan
[12]Duke Translational Medicine Institute, Duke University Medical Center, Durham, North Carolina, USA

Contributors JJM and RMC conceived the idea of the study. All authors provided input into the data interpretation and analysis. SMH, RRH, RMC and JJM are members of the NAVIGATOR Executive Committee; LAL, TM, GER, GT, FAM and FTC are members of the NAVIGATOR Steering Committee; and ES acted on the Data Safety Monitoring Board. LET and JLS performed the statistical analyses. DP, RMC and JJM drafted the manuscript; LET, JLS, SMH, RRH, ES, LAL, TM, GER, GT, FAM and FTC critically revised the manuscript. All authors gave final approval for submission of the manuscript.

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